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Iopamidol Injection

General Notices

Action and use

Iodinated contrast medium.

DEFINITION

Iopamidol Injection is a solution of Iopamidol in Water for Injections with or without excipients.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of iopamidol, $C_{17}H_{22}I_3N_3O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dry 1 mL of the injection over *phosphorus pentoxide* at a pressure of 2 kPa for 16 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of iopamidol (*RS 441*).
B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (5).

TESTS

Acidity or alkalinity

pH, 6.5 to 7.5, Appendix V L.

Light absorption

The *light absorption* of a 4-cm layer of the injection, Appendix II B at 450 nm is not more than 0.120.

Free aromatic amines

The following solutions and reagents are stored in ice-water and protected from bright light.

Mix a volume of the injection containing 0.5 g of Iopamidol with *water* and add sufficient *water* to produce 20 mL. Place the solution in ice-water, protected from light, for 5 minutes. Add 1.0 mL of *hydrochloric acid*, mix and allow to stand for 5 minutes. Add 1.0 mL of a 2% w/v solution of *sodium nitrite* prepared immediately before use, mix and allow to stand for 5 minutes. Add 1.0 mL of a 12% w/v solution of *ammonium sulfamate*, swirl gently until gas liberation has ceased and allow to stand for 5 minutes. Add 1.0 mL of a freshly prepared 0.1% w/v solution of *naphthylethylenediamine dihydrochloride* and mix. Remove from the ice-water and allow to stand for 10 minutes. Add sufficient *water* to produce 25 mL and mix.

Immediately measure the *absorbance* at 500 nm, Appendix II B, using in the reference cell a solution prepared by treating 20 mL of *water* in the same manner.

The *absorbance* is not greater than that obtained by treating 20 mL of a 0.00125% w/v solution of *iopamidol impurity A EPCRS* in *water* in the same manner and beginning at the words “Place the solution…”.(500 ppm).

Free iodine

Mix a volume of the injection containing 2.0 g of Iopamidol with *water* and add sufficient *water* to produce 25 mL. Add 5 mL of *toluene* and 5 mL of *dilute sulfuric acid*, shake and centrifuge. Any red colour in the upper phase is not more intense than that of the upper phase obtained in the same manner from a mixture of 22 mL of *water*, 2 mL of *iodide standard solution (10 ppm I)*, 5 mL of *dilute sulfuric acid*, 1 mL of *hydrogen peroxide solution (100 vol)* and 5 mL of *toluene* (10 ppm).

Iodide

To 10 mL of the injection add sufficient *water* to produce 50 mL. Add 2.0 mL of *0.001M potassium iodide*. Carry out the method for *potentiometric titration*, Appendix VIII B, using 0.001M *silver nitrate VS*, a silver indicator electrode and an appropriate reference electrode. Subtract the volume of titrant corresponding to the 2.0 mL of *0.001M potassium iodide*, determined by titrating a blank to which is added 2.0 mL of 0.001M *potassium iodide*, and use the residual value to calculate the iodide content.

1 mL of *0.001M silver nitrate VS* is equivalent to 126.9 µg of iodide.

Not more than 2.0 mL of *0.001M silver nitrate VS* is required (40 ppm).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a volume of the injection containing 0.5 g of Iopamidol with *water* and add sufficient *water* to produce 50 mL.
(2) 0.005% w/v of *iopamidol impurity H EPCRS* in *water*.
(3) Dilute 1 volume of solution (1) to 500 volumes with *water*.
(4) To 200 volumes of solution (2) add 1 volume of solution (1) and add sufficient *water* to produce 500 volumes.
(5) 1.0% w/v of *iopamidol EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use two stainless steel columns (25 cm × 4.6 mm) coupled in series and packed with *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-Phenyl 80 Å is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

The retention time of iopamidol is about 15 minutes and the retention time of the peak due to impurity H is about 13 minutes. Impurity H and impurity I have identical retention times.

MOBILE PHASE

Mobile phase A *water*.

Mobile phase B Equal volumes of *acetonitrile* and *water*.

Equilibrate the column for at least 20 minutes with mobile phase A.

Time (Minutes)	Mobile phase A (%v/v)	Mobile phase B (%v/v)	Comment
0-18	100	0	isocratic
18-40	100→62	0→38	linear gradient
40-45	62→50	38→50	linear gradient
45-50	50→100	50→0	linear gradient
50-60	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to iopamidol and iopamidol impurity H is at least 2.0. If necessary, adjust the composition of the mobile phase or the time programme of the gradient.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H or impurity I is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of any *secondary peaks* other than impurites H and I is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

Sterility

Complies with the *test for sterility*, Appendix XVI A.

Bacterial endotoxins

The endotoxin limit concentration is 0.7 IU per mL, Appendix XIV C.

ASSAY

Mix a volume of the injection containing 0.220 g of Iopamidol with *water* and add sufficient *water* to produce 20 mL. Add 5 mL of *strong sodium hydroxide solution*, 1 g of *zinc powder* and a few glass beads. Boil under a reflux condenser for 30 minutes. Allow to cool and rinse the condenser with 20 mL of *water*, adding the rinsings to the flask. Filter through a sintered-glass filter and wash the filter with several quantities of *water*. Collect the filtrate and washings. Add 5 mL of *glacial acetic acid* and titrate immediately with *0.1M silver nitrate VS*. Carry out the method for *potentiometric titration*, Appendix VIII B, using a suitable electrode system such as silver-silver chloride.

Each mL of *0.1M silver nitrate VS* is equivalent to 25.90 mg of $C_{17}H_{22}I_3N_3O_8$.

STORAGE

Iopamidol Injection should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of Iopamidol and as the equivalent amount of iodine.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Iopamidol.